

April 7, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 17218-edited.doc).

Title: Clinical features of second primary cancers arising in early gastric cancer patients after endoscopic resection

Author: Jung-Wook Kim, Jae-Young Jang, Young Woon Chang, Yong Ho Kim

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 17218

I am really appreciative of Editor's and reviewers' thoughtful and constructive comments. We have revised the manuscript that includes additional explanations as recommended by the reviewers. I hope that my endeavor to address these issues is satisfactory to both Editor and the reviewers. Again, on behalf of our authors, thank you.

Reviewer Comments:

Reviewer #1: The manuscript submitted by Kim et al. evaluates a set of gastric cancer patient data in regards to early and advanced stage gastric cancer and second primary cancer development incidence and location. The manuscript overall is well written and I recommend publication after careful consideration of the following points:

Q1. Language and diction should be corrected, especially the use of the word clinicopathological is unusual. I do not know what this means?

Answers: Thank you for your careful comment. As you pointed out, we changed or eliminated the word "clinicopathological" from the manuscript.

Q2. Clear definitions of abbreviations the first time they are mentioned in the text (SPCs was

not explained, EGC is mentioned in multiple places, etc.)

Answers: We are sincerely sorry about an inadvertent mistake. As you commented, we defined abbreviations at the first time they are mentioned in the manuscripts. And, we highlighted changes to the manuscript.

Q3. How did the researcher determine that the SPC was indeed an independent second cancer that did not develop as a metastasis? Was any marker analysis done to see if dedifferentiated cells from the gastric epithelium were present in the second primary cancer?

Answers: As we described in Methods section, the diagnostic criteria of Warren and Gates were used to diagnose second primary cancer. Additionally, we often used immunohistochemical stains to differentiate SPCs from the metastasis of primary gastric cancer. So, we have added this issue in “Methods” section as follows.

“If necessary, immunohistochemical stains were used to differentiate SPCs from the metastasis of primary gastric cancer.”

Q4. The authors mention in their discussion that EGC and AGC may represent different stages of the same cancer - but that cannot be the case in the same patient from this data set, correct? This should be clarified.

Answers: We completely agree with your comments. As you pointed out, our mention in “Discussion” section may be irrelevant, judging by our results. Therefore, we carefully revised the text in the “Discussion” section as follows.

“However, our results suggest the possibility that it makes no genetic difference contributing the development of SPC between EGC and AGC, because the SPC incidence after complete resection of the tumor was identical in the two groups.”

Q5. Figure 2 is obsolete since figure 3 contains a clear distinction between the tumor locations - the only non-solid tumor was of hematological origin.

Answers: Thank you for your careful comment. As you recommended, we removed figure 2. Thanks again.

Reviewer #2: Dear Editor, This is well designed and correct statistical analysis performed study. I just want to remind to the authors to add the p value for genders in Table 1. Regards

Answers: Thank your careful comments. We are very sorry that you were confusing Table 1. We rearranged the p value for genders in Table 1 as follows.

Table 1 Characteristics of the EGC and AGC groups

	Overall (<i>n</i> = 413)	EGC group (<i>n</i> = 184)	AGC group (<i>n</i> = 229)	<i>P</i> value
Mean age (mean \pm SD, years)	61.3 \pm 11.6	62.1 \pm 10.2	60.8 \pm 12.6	0.263
Gender, <i>n</i> (%)				
Male	293 (70.9)	137 (74.5)	156 (68.1)	<u>0.159</u>
Female	120 (29.1)	47 (25.5)	73 (31.9)	
Smoking, <i>n</i> (%)	229 (55.4)	110 (59.8)	109 (47.6)	0.014
Alcohol, <i>n</i> (%)	190 (46.0)	97 (52.7)	93 (40.6)	0.014
<i>H. pylori</i> infection, <i>n</i> (%)	258 (62.5)	105 (57.1)	153 (66.8)	0.042
Histology, <i>n</i> (%)				
Differentiated	262 (63.4)	184 (100)	78 (34.1)	< 0.001
Undifferentiated	151 (36.6)	0	151 (65.9)	
Follow-up duration (mean \pm SD, months)	37.2 \pm 15.9	36.9 \pm 14.9	37.4 \pm 16.7	0.697

EGC: Early gastric cancer; AGC: Advanced gastric cancer; SD: Standard deviation; *H. pylori*: *Helicobacter pylori*.

Thank you again.

Sincerely yours,

A handwritten signature in black ink, appearing to be 'JY' or 'Jang', written in a cursive style.

Jae-Young Jang, MD, PhD

Division of Gastroenterology, Department of Internal Medicine, College of Medicine, Kyung Hee University, 1 Hoegi-dong, Dongdaemoongu, Seoul, 130-702, Korea.

Tel: +82-2-958-8200, Fax: +82-2-968-1848

E-mail: jjjang@khu.ac.kr